

temporal artery is clamped at its lowest point and before it ramifies into numerous smaller vessels, whereas in the curved incision the many branches of the temporal artery are severed individually and each one must be clamped separately; again, it is easier to enlarge the bony opening downward to the base of the skull when the vertical incision is used—an important point for drainage in cases of fracture of the skull. To preserve the strong attachment of the temporal muscle to the parietal crest is difficult and even impossible when the usual curved incision is used; in this manner the decompression may so weaken the side of the head that a hernia cerebri appears as the intracranial pressure increases; especially is this true in irremovable tumors of the brain; this complication is a most rare occurrence following a decompression performed with the vertical incision and a careful regard for the attachment of the temporal muscle.

CONCLUSIONS. The operation of cranial decompression is one that should be used much more frequently than it is at present; especially is this true in the conditions of brain tumor, fracture of the skull, brain abscess, and selected cases of spastic paralysis due to an intracranial hemorrhage at birth.

The subtemporal method of cranial decompression is the ideal route; besides being less difficult technically it exposes an area of the brain most frequently involved. This permanent decompression opening does not weaken the skull in that the thick overlying temporal muscle protects it most adequately, so that herniæ cerebri are not to be feared.

The operative mortality is low. Patients with intracranial conditions should not be permitted to become blind or to reach the dangerous stage of medullary compression without a subtemporal decompression being performed early.

FRACTURE OF THE BASE OF THE SKULL WITH ESCAPE OF CEREBROSPINAL FLUID FROM THE EAR. THE EFFECT OF ATROPINE AND EPINEPHRIN UPON THE SECRETION.¹

BY J. WALKER MOORE, M.D.,
LOUISVILLE, KENTUCKY.

The purpose of this paper is threefold:

1. To report a case of fracture of the base of the skull with the escape of an unusual amount of cerebrospinal fluid from the ear.

¹ I have to thank Dr. Charles H. Frazier most cordially in making it possible for me to carry out the work presented in this paper, and freely placing at my disposal valuable unpublished data concerning the effects of the injection of certain saline extracts of the body organs upon the secretion of cerebrospinal fluid in dogs.

2. To outline briefly the evolution of the hypothesis that the cerebrospinal fluid is a true secretion.

3. To present the effect both chemically and clinically of the hypodermic injection of atropin and epinephrin upon the secretion of cerebrospinal fluid.

Fracture of the base of the skull with the escape of cerebrospinal fluid from the cranium has been observed for centuries. Bidloo the elder (quoted by St. Clair Thomson), writing in the latter half of the seventeenth century, reported a case of a patient who had a fracture of the bridge of the nose followed by a continuous flow of clear watery fluid from the right nostril; twenty ounces of this fluid escaped in twenty-four hours. Stalpartius von der Wiel, in 1725, published a case in which a large quantity of clear watery fluid escaped from the ear after a severe injury to the head. Matthei and others have collected a number of such cases. Indeed, judging from the recent literature, surgeons do not look upon this as a matter of rare occurrence.

The case which we have to report is not a unique one by any means, however, judging from his age, weight, and stature; the amount of cerebrospinal fluid that escaped from the ear at regular intervals is rather remarkable.

CASE I.—W. R., Episcopal Hospital, aged six years, male; weight thirty-five pounds.

Eighteen hours before admission into the hospital the child fell down a flight of stairs backward while attempting to catch a ball that he had thrown upward. The screams attracted the mother's attention. She found the child lying on the floor, in an unconscious condition, bleeding from the left ear. Within a few minutes blood and clear colored fluid flowed alternately from the left ear. Later (about twenty minutes) the blood ceased entirely, but the clear colored fluid continued to flow, with occasional momentary stoppage up to the time of admission into the hospital. The child remained unconscious for six hours after the accident; thereafter was conscious of things around him. He vomited just after the fall and again six hours later.

The child was of instrumental delivery. Since the age of eight months the patient has had frequent epileptic seizures, the attacks occurring at irregular intervals. The child may go as long as three days without a seizure, on the other hand the attacks may occur daily, or several times during the day, and continue in this manner for two or three days. The oncoming attack is usually ushered in by the child being peevish, fretful, restless, spitting, etc. Then comes the seizure which manifests itself by a rapid contraction of arms and legs, a sudden scream and a falling to the floor, rapidly becoming cyanotic and blue in the face. At times the child froths at the mouth but never bites his tongue. The attack is usually three minutes in duration. The child, according to the parents,

is bright and has a wonderful memory. No history of mental deterioration. Had a discharging right ear two weeks ago which rapidly cleared up under treatment. Mother states that the child did not have an epileptic seizure before the fall, nor were there any symptoms of an attack following the accident.

On admission to the hospital, eighteen hours after the accident, the examination revealed a fairly well-nourished child of six years, somewhat restless, but nothing more than one would expect of a child in a strange place. The child would heed immediately when his name was called, and would protrude the tongue or raise the arm when asked to; we were unable to draw the patient into a conversation, but he would at intervals articulate words, as water, mother, and the like. However, he would never utter a complete sentence.

Aside from the discharging left ear the physical examination was essentially negative. There were no signs of injury to the scalp. Eyes reacted promptly to light, pupils were equal. Ocular movements normal. Cardiac action was rapid, pulse of good tension and volume. Lungs, abdomen, and extremities were negative.

The patella, achilles, biceps, and triceps reflexes reacted promptly but were not increased. There were no palsies, no ankle-clonus. Skin reflexes and sensation normal.

Temperature, 97°; pulse, 130; respiration, 24.

From the left ear could be seen a continuous flow of clear watery fluid. The flow was so rapid that within a short time the pillow-cover in the region of the head would be soaked with the fluid. The fluid reduced Fehling's solution. Specific gravity, 1007. One c.mm. showed 1730 red blood corpuscles, 49 polymorphonuclear leukocytes, and 39 lymphocytes.

March 16. The child is quiet, lies with the right side of the head on the pillow. The left ear continues to discharge a clear watery fluid at irregular intervals; that is to say, the flow ceases an hour or more, two or three times in the twenty-four hours.

The child had a convulsion which lasted two minutes; during the convulsion the lips became cyanosed, face pinched, upper and lower extremities contracted rapidly. There was no frothing at the mouth nor biting of the tongue. Had to be catheterized. Temperature, 103; pulse, 135; respiration, 24.

March 17. Very little change in condition. The child drinks a great deal of water and takes liquid diet well.

The ear continues to discharge at irregular intervals. Had a convulsion, similar to the one on the previous day. No record was made of the amount of secretion during the convulsion, but the attending nurse states that there was not a noticeable increase during the convulsion, judging from the wet spot on the pillow cover.

March 18. The ear ceased secreting only once during the twenty-four hours, and that was for about three hours, while

the child was asleep. There is a suggestive Kernig and reflex resistance of the neck muscles to flexion of head. The right ear began to discharge mucopurulent material. Secretion collected from the left ear by means of an eye dropper in sixty minutes was 15 c.c.

The eye-grounds were examined by Dr. Bromley. The report was as follows:

O. D. Nerve circumscribed and flat; very little venous congestion. Media clear.

O. S. Slight engorgement of veins, nerve perfectly flat and circumscribed. No edema of retina. Media clear.

March 19. Patient takes water and liquid nourishment freely. The fluid collected from the ear in sixty minutes amounted to 21 c.c. The child dropped off to sleep and the ear stopped secreting for hours. On awakening the ear began secreting again.

Ten grains of urotropin were given, and fluid collected every five minutes for two hours and placed in separate test-tubes. We were unable to demonstrate the presence of urotropin with the bromine water test in the fluid collected.

Blood Count. White blood corpuscles, 17,200; polynuclears, 66 $\frac{2}{3}$ per cent., mononuclears, 3 per cent.; transitionals, 7 $\frac{2}{3}$ per cent.; lymphocytes, 22 $\frac{1}{3}$ per cent.; eosinophiles, 1 per cent.

March 21. Very little change in condition of patient. Kernig's sign suggestive. No rigidity of neck.

March 23. Child is quiet most of the time, occasionally becoming restless. Kernig is positive. No rigidity of neck; no bowing of back.

March 24. The child is quite restless at times. There is rigidity of the neck muscles, with slight retraction of the head. Kernig's sign is positive. No bowing of the back. Pulse is rapid; secretion from left ear is scanty.

Blood Count. White blood corpuscles, 25,350; polynuclears, 79 per cent.; transitionals, 3 per cent.; lymphocytes, 18 per cent.

March 25. The patient appears to be in great agony, crying out at frequent intervals; retraction of neck is marked; there is also bowing of the back, with drawing up of lower extremities. The left ear has ceased secreting entirely. Skin is dry; eyes sunken; tongue parched; radial pulse scarcely perceptible.

From this point the patient rapidly went downward, and died March 28.

The autopsy was performed by Dr. C. Y. White, director of the pathological laboratory of the Episcopal Hospital. He reports as follows:

The dura is transparent, the inner surface being smooth and glistening. The vessels of the pia mater are only slightly congested. No macroscopic evidence of a meningitis. No edema beneath the pia.

On severing the brain from the cord an excessive amount of cerebrospinal fluid escaped into the base of the skull.

The dura is entirely stripped for the purpose of examining the skull, and there is found a fracture involving the squamous and anterior surface of the petrous portion of the left temporal bone. That part of the fracture involving the petrous portion is Y-shape, and extends into the internal auditory meatus. One limb of the Y begins with the depression for the Gasserian ganglion; the other with the opening for the small petrosal nerve. The two uniting just external to the Hiatus Fallopii and running outward parallel with and $\frac{1}{8}$ of an inch beneath the superior border to the squamous portion, where it continues directly upward in that bone for one inch.

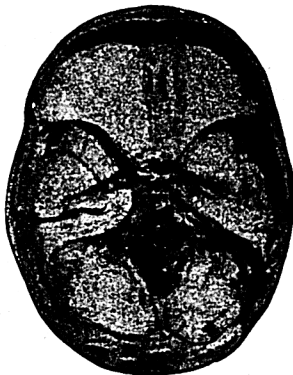


Figure showing the Y-shaped fracture involving the petrous portion of the left temporal bone. The fracture was outlined with lead pencil and a photograph taken of the bone of skull.

Dr. W. B. Cadwalader made numerous sections of the brain and choroid plexus, and submits the following report:

Sections were made from various parts of the cerebral cortex and the cerebellum. For the most part they were entirely negative, but here and there in some sections a few polymorphonuclear leukocytes could be seen infiltrating the pia, and grouped about some of the smaller bloodvessels within the fissures of the cortex. This was a real meningitis, yet it was so slight that it would require more than a superficial examination to find it. Sections from the basal ganglia, internal capsule, pons cerebellum, and different levels of the spinal cord appear to be entirely normal. There were no evidences of meningitis in these parts and the tissue stained

normally with the Weigert stain. Sections of the choroid plexus were made and were stained by a number of different methods. All the cells appeared entirely normal. I could not demonstrate some of the granules which are thought to react differently to stains, and which have been supposed to have some relationship to secretory functions. Comparing the sections taken from this case with similar sections of two other brains which ought not to have had any disease of the choroid plexus, I could not really find any difference. On the whole it is just to conclude that this specimen, brain and cord, shows absolutely nothing abnormal except a very mild and diffuse infiltration of the pia which was probable of recent origin.

THE EVOLUTION OF THE HYPOTHESIS THAT THE CEREBROSPINAL FLUID IS A TRUE SECRETION. The hypothesis that the cerebrospinal fluid is a secretory product of the choroid plexus has been the source of infinite research for a number of decades. Leonard Hill,² in the early 90's, advocated the hypothesis that the fluid is a serous transudation from the capillaries of the vascular choroid. He regards the cerebrospinal fluid as the lymph of the brain, its secretion and resorption being explained on the same lines as other lymphatic exudate. He contends that the secretion of the fluid increases with the rise in cerebral capillary pressure and the latter varies directly and absolutely with vena cava pressure. He cites a case of St. Clair Thomson's in which there was a continuous flow of cerebrospinal fluid from the left nostril. At the invitation of St. Clair Thomson³ he made the following observations:

I.

1. Patient sitting quietly, and in five minutes 23 m. were collected.
2. Patient sitting and straining, and in five minutes 35 m. were collected.
3. Patient sitting quietly, and in five minutes 19 m. were collected.
4. Patient sitting and straining, and in five minutes 33 m. were collected.
5. Patient lying—lying down and not straining, 27 m. were collected.
6. Patient sitting with head overhanging in five minutes, 28 m. were collected.
7. Patient sitting with head forward, and in five minutes 15 m. were collected.

II.

1. Abdomen compressed, and in five minutes 27 m. were collected.
2. Sitting quietly, and in five minutes 14 m. were collected.

² The Cerebrospinal Fluid, Allbutt's System of Medicine, 1899, vii, 239.

³ Ibid., New York, 1899.

3. Abdomen compressed, and in five minutes 24 m. were collected.
4. Sitting quietly, and in five minutes 23 m. were collected.

The experiments carried out by Hill are valueless, owing to the short space of time given to each procedure.

It is stated that the normal amount of cerebrospinal fluid present in the subarachnoid space is about 100 c.c. That this fluid is rapidly formed is shown by the enormous amount of fluid escaping from the ear of my patient. It is clear that any condition which would cause congestion of the cerebral vessels would mechanically encroach upon the subarachnoid space, thereby increasing intracranial pressure. A sudden increase of flow after straining or compressing the abdomen, and a decrease in flow when the mechanical pressure is released, is to be expected. Suffice it to say, if the straining or compression of the abdomen had been kept up for twenty to thirty minutes, Hill's observations would have been different, as will be shown later. Furthermore, Sabin has shown that the subarachnoid space is fully developed, long before the lymphatics have budded out from the subclavian and iliac veins.

Mott⁴ is credited with giving the following compositions of the fluid, which he considered to be against its being a transudation from the blood or a lymphatic secretion.

1. It contains 0.02 per cent. of proteins against 7 per cent. in blood plasma and 4.5 per cent. in body lymph.
2. There is an absence of lipochroma.
3. There are no leukocytes in normal cerebrospinal fluid.
4. In enteric fever there is an absence of agglutination.
5. It has no hemolytic action on the blood corpuscles of other animals.
6. It contains no alexins.

Willis, in 1664, first mentioned the glandular appearance of what is now called the choroid plexus. Faivre, in 1853, maintained that the cuboidal cells which cover the choroid plexuses are secreting cells concerned in the formation of cerebrospinal fluid. Mott examined histologically the choroid plexus of a human subject. He reports that the sections under high power reveal tufts of vessels surrounded by a loose connective tissue covered by a single layer of cubical, spheroidal or polyhedral cells lying on a basement membrane. Around the arteries and arterioles and lying in the loose connective tissue numerous nerve fibers are seen in a form of a plexus. In the sections he also observed vacuoles in the cells, and cup-like cavities in others, as one would expect if fluid had escaped from the vacuole. He concludes, therefore, from the histological evidence that the choroid plexus is a gland with an external secretion, but with an internal destination. Being a mixed gland, he suggests

⁴The Physical and Chemical Properties of the Cerebrospinal Fluid, Oliver Sharpey's Lectures, *Lancet*, July 2 and 9, 1910.

that its mode of formation is in an inverse manner to those formed by epithelial invagination of glands with an excretory duct. Ependymal invagination occurs for the choroid plexus.

Kramer⁵ describes the histological appearance of the choroid plexus as highly vascular projections of the pia mater into the ventricle, covered with villous-like projections about 1 to 2 mm. in diameter, under the microscope these villi are seen to be made up of a number of secondary villi about 25 mm. in diameter, which again show grape-like projections. Through the centre of the villi run comparatively thick-walled bloodvessels, giving the organ a highly vascular appearance. The connective tissue of the villi is that of the pia mater. Covering the villi of the plexus is a layer of spheroidal cells in each of which may be seen in addition to the nucleus, yellowish granules. These cells are probably the secreting cells of the organ. These cells are without ducts, pouring their secretions directly into the ventricular system of the brain.

Carl Schmidt, in 1850, advanced the chemical evidence in favor of a true secretion. Petit and Girard,⁶ in 1902, demonstrated the secretory functions of the choroid plexus in different classes of vertebrates. They found that administration of substances endowed with hypersecreting action caused histological changes in the cells covering the plexus. Dixon and Halliburton have experimental proof that an intravenous injection of an extract of choroid plexus produces an increased secretion of the cerebrospinal fluid. The injections of extracts of the brain produces the same effect upon the respiration, blood-pressure and flow of the cerebrospinal fluid, as does the injection of extract of choroid plexus. So also in cases of general paralysis and brain softening, where destructive processes are actively taking place, the cerebrospinal fluid when injected, produces identical effects. They suggest, therefore, that the increase in output of fluid is due to the stimulating action of some chemical substance (hormone) in the extract on the secreting cells of the gland, and that the hormone is a product of the brain's metabolism which passes to the choroid plexus and stimulates the secreting cells of the plexus.⁷

Writers as Levy, Cushing, Obersteiner, Cavaggani, Frazier, and others likewise maintain the secretory activity of the choroid plexus as the formation of cerebrospinal fluid.

The following observations were made in the case of the patient herein reported:

⁵ Fall of Pressure Produced by Choroid Extract, Jour. Amer. Med. Assoc., 1911, lvi, 265.

⁶ Smith, E., The Cerebrospinal Fluid, Guy's Hosp. Gaz., London, 1911, xxv, 141.

⁷ W. Mestregat, in a recent publication, expresses his belief that the cerebrospinal fluid is neither a transudation nor a secretion, but is a product of dialysis from the blood plasma.

TABLE I.

Time	Amount collected in five minutes approximate in c.c.	State of patient.	Heart rate	Analyses of cerebrospinal fluid.					Expressed as grams per 100 c.c. fluid.		
				Duration, minutes.	Actual amt. c.c.	Solids, gm.	Ash gm.	K ₂ O gm.	Solids.	Ash.	K ₂ O.
Period I—Control											
11.05	.73 c.c. (12 m.)	Apparently asleep	126	30	5.4	0.0720	0.0194	0.0008	1.35	0.91	0.015
11.10	1.54 c.c. (25 m.)	Apparently asleep	130								
11.15	1.23 c.c. (20 m.)	Apparently asleep	128								
11.20	.48 c.c. (8 m.)	Apparently asleep	130								
11.25	.49 c.c. (8 m.)	Apparently asleep	128	40	4.4	0.0676	0.0476	0.0009	1.54	1.08	0.017
11.30	.86 c.c. (14 m.)	Apparently asleep	126								
Period II ^a											
5	.73 c.c. (12 m.)	Restless and quiet	170								
10	.37 c.c. (6 m.)	Restless and quiet	140								
15	.30 c.c. (5 m.)	Restless and quiet	163	25	7.2	0.0751	0.0501	0.0009	1.04	0.70	0.013
20	.37 c.c. (6 m.)	Restless and quiet	134								
25	.73 c.c. (12 m.)	Restless	170								
30	.55 c.c. (9 m.)	Restless and quiet	147								
35	.37 c.c. (6 m.)	Quiet	136	20	4.75	0.0587	0.0379	0.0006	1.24	0.80	0.013
40	.86 c.c. (14 m.)	Quiet	140								
Period III											
45	.96 c.c. (16 m.)	Quiet	140								
50	1.50 c.c. (25 m.)	Restless and quiet	136	90	Not measured	0.0614	0.0392	0.0007	0.92	0.59	0.009
55	1.38 c.c. (23 m.)	Quiet	136								
60	1.68 c.c. (28 m.)	Restless and quiet	168								
65	1.38 c.c. (23 m.)	Restless	163								
Period IV				30	7.0	0.0648	0.0414	0.0006	0.92	0.59	0.009
70	1.20 c.c. (20 m.)	Restless	164								
75	1.14 c.c. (19 m.)	Restless	164								
80	1.02 c.c. (17 m.)	Restless	164								
85	1.20 c.c. (20 m.)	Restless	166	30	7.1	0.0930	0.0624	0.0011	1.31	0.88	0.016
Period V											
P.M.	Not measured	...	90								
2.35	Period VI										
5	1.14 c.c. (19 m.)	Quiet	140	65	13	0.1530	0.1022	0.0014	2.73	1.82	0.025
10	1.14 c.c. (19 m.)	Quiet	138								
15	1.20 c.c. (20 m.)	Quiet and restless	145								
20	.96 c.c. (16 m.)	Quiet	138								
25	1.02 c.c. (17 m.)	Quiet	140	110	6.9	0.1096	0.0632	0.010	1.59	0.92	0.014
30	1.20 c.c. (20 m.)	Quiet	140								
Period VII											
35	1.08 c.c. (18 m.)	Apparently asleep	140								
40	.96 c.c. (16 m.)	Apparently asleep	138	45	13.4	0.1612	0.1065	0.0015	1.20	0.80	0.011
45	1.14 c.c. (19 m.)	Quiet	140								
50	1.14 c.c. (19 m.)	Quiet	138								
55	1.38 c.c. (23 m.)	Restless	144								
60	1.14 c.c. (19 m.)	Restless	144	110	6.9	0.1096	0.0632	0.010	1.59	0.92	0.014
Period VIII											
P.M.	Not measured	...	65								
5	.30 c.c. (5 m.)	Restless	150								
10	.12 c.c. (2 m.)	Apparently asleep	140	45	13.4	0.1612	0.1065	0.0015	1.20	0.80	0.011
15	0.0	Apparently asleep	138								
20	0.0	Apparently asleep	136								
25	0.0	Apparently asleep	136								
30	1.02 c.c. (17 m.)	Restless	140	45	13.4	0.1612	0.1065	0.0015	1.20	0.80	0.011
35	1.80 c.c. (30 m.)	Apparently asleep	140								
40	1.38 c.c. (23 m.)	Apparently asleep	140								
45	1.32 c.c. (22 m.)	Restless	150								

^a Epinephrin (1 to 1000) 5 m. injected subcutaneously. A blanching appeared at point of injection.

TABLE I—Continued.

Time	Amount collected in five minutes approximate in c.c.	State of patient.	Heart rate.	Analyses of cerebrospinal fluid.					Expressed as grams per 100 c.c. fluid.		
				Duration, minutes.	Actual amt., c.c.	Solids gm.	Ash gm.	K ₂ O gm.	Solids.	Ash.	K ₂ O.
Period XI											
5	.80 c.c. (15 m.)	Quiet	144								
10	1.20 c.c. (20 m.)	Restless	150								
15	1.14 c.c. (19 m.)	Quiet	142								
20	1.14 c.c. (19 m.)	Quiet	140								
25	1.02 c.c. (17 m.)	Quiet	138								
30	.96 c.c. (16 m.)	Quiet	150								
35	1.14 c.c. (19 m.)	Restless	154								
40	.90 c.c. (15 m.)	Quiet	150								
45	.84 c.c. (14 m.)	Quiet	157	75	14.5	0.1607	0.0931	0.0013	1.10	0.62	0.009
50	.96 c.c. (16 m.)	Restless	170								
55	.84 c.c. (14 m.)	Restless	168								
60	.60 c.c. (10 m.)	Restless	168								
65	.60 c.c. (10 m.)	Restless	166								
		Was given water									
70	.84 c.c. (14 m.)	Quiet	150								
75	.84 c.c. (14 m.)	Apparently asleep	140								
Period XII											
80	1.50 c.c. (30 m.)	Apparently asleep	140								
85	2.10 c.c. (35 m.)	Apparently asleep	138								
90	.84 c.c. (14 m.)	Apparently asleep	140								
95	1.20 c.c. (20 m.)	Restless	140								
100	.90 c.c. (15 m.)	Restless	144	45	12.4	0.1131	0.645	0.0008	0.91	0.52	0.006
105	.84 c.c. (14 m.)	Quiet	150								
110	1.14 c.c. (19 m.)	Restless	154								
115	1.50 c.c. (25 m.)	Quiet and restless	145								
120	1.50 c.c. (25 m.)	Quiet and restless	148								

AVERAGE OF PERIOD.

	Solids.	Ash.	K ₂ O
I	1.35	0.91	0.015
II to X (except V)	1.38	0.91	0.014
XI and XII	1.02	0.59	0.008

PERCENTAGE OF ASH IN TERMS OF TOTAL SOLIDS.

I	68.6	V	63.9	IX	57.8
II	71.9	VI	63.9	X	66.1
III	66.7	VII	67.3	XI	55.1
IV	61.6	VIII	66.8	XII	57.0

AVERAGE.

I	68.6	II to X (inc. V)	65.3	XI to XII	57.7
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The table summarizes the amount of fluid excreted in five consecutive minutes, the state of the patient, whether quiet, restless or apparently asleep and the heart rate. (The heart rate was taken twice in each five minute period, with a stethoscope, and the average recorded.) The fluid was collected in sterile glass test-tubes, labeled periods I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII. The tubes were given to Dr. Charles H. Frazier, who in turn secured the valuable service of Dr. A. E. Taylor, professor of physiological chemistry in the University of Pennsylvania, for chemical analysis.

March 20. Epinephrin (1 to 1000) 5 m. injected subcutaneously into the arm. Eight hours and forty minutes later atropin sulphate, gr. $\frac{1}{250}$, was injected hypodermically. Experiment begun at 11 A.M.

TABLE II.

At 3.35 water, 5iv, given by mouth, and twenty-five minutes later atropin sulphate, gr. $\frac{1}{32}$, hypodermically.

Time.	Approximate amount in c.c.	State of patient.	Heart rate.
2:35			
5	2.70 c.c. (45 m.)	Quiet	134
10	2.70 c.c. (45 m.)	Quiet	130
15	2.40 c.c. (40 m.)	Quiet	134
20	2.70 c.c. (45 m.)	Quiet	132
3:00	Atropin, 0.05 gr. hypodermically.		
5	2.40 c.c. (40 m.)	Restless	140
10	1.50 c.c. (25 m.)	Restless	145
15	1.50 c.c. (25 m.)	Quiet	138
20	1.50 c.c. (25 m.)	Quiet	136
25	.96 c.c. (16 m.)	Quiet and restless	138
30	1.14 c.c. (19 m.)	Quiet and restless	136
35	1.32 c.c. (22 m.)	Quiet and restless	138
40	1.08 c.c. (18 m.)	Apparently asleep	138
45	1.26 c.c. (21 m.)	Apparently asleep	140
50	1.14 c.c. (19 m.)	Apparently asleep	138
55	.90 c.c. (15 m.)	Apparently asleep	140
60	.90 c.c. (15 m.)	Apparently asleep	138
65	.96 c.c. (16 m.)	Apparently asleep	144
70	.60 c.c. (10 m.)	Apparently asleep	140
75	.90 c.c. (15 m.)	Apparently asleep and restless	144
80	1.02 c.c. (17 m.)	Apparently asleep	138
85	.90 c.c. (15 m.)	Apparently asleep	138
Milk is given.			
90	.66 c.c. (11 m.)	Restless	145
95	1.38 c.c. (23 m.)	Restless	146
100	1.32 c.c. (22 m.)	Restless	144
105	—	Exceedingly restless	...
110	.96 c.c. (16 m.)	Restless	146
115	.96 c.c. (16 m.)	Restless	144
120	.90 c.c. (15 m.)	Restless	150

TABLE III.—TO SHOW THE INFLUENCE OF SLEEP, QUIET, AND RESTLESSNESS UPON THE SECRETION OF CEREBROSPINAL FLUID, MARCH 22.

Time.	Approximate amount collected in 5 minutes in c.c.	State of patient.	Heart rate.
11:00	.30 c.c. (5 m.)	Quiet	134
5	1.08 c.c. (18 m.)	Quiet and restless	134
10	1.08 c.c. (18 m.)	Quiet	135
15	.60 c.c. (10 m.)	Restless and Quiet	145
20	.90 c.c. (15 m.)	Quiet	134
25	.90 c.c. (15 m.)	Quiet	140
30	.96 c.c. (16 m.)	Quiet	140
35	1.14 c.c. (19 m.)	Quiet	138
40	1.38 c.c. (23 m.)	Quiet and restless	144
45	1.14 c.c. (19 m.)	Quiet and restless	142
50	1.08 c.c. (18 m.)	Quiet	134
55	1.50 c.c. (25 m.)	Quiet	136
60	1.14 c.c. (19 m.)	Quiet and restless	140
65	1.08 c.c. (18 m.)	Quiet and restless	144

COLLECTED THE FOLLOWING DAY, MARCH 23.

11:00 A.M.			
5	.90 c.c. (15 m.)	Quiet and restless	140
10	.84 c.c. (14 m.)	Quiet and restless	138
15	1.02 c.c. (17 m.)	Quiet and restless	140
20	2.28 c.c. (38 m.)	Quiet	138
25	1.38 c.c. (23 m.)	Quiet and restless	142
30	.93 c.c. (15 m.)	Restless	150
35	.96 c.c. (16 m.)	Restless	144

A SUMMARY OF THE EFFECT OF ATROPIN ON CEREBROSPINAL FLOW.—Table I. The normal secretion during one hour amounted to 17.7 c.c., average heart rate was equal to 139 beats per minute. After the injection of atropin, gr. $\frac{1}{250}$ hypodermically, the amount of secretion during one hour amounted to 11.8 c.c., a decrease of 5.9 c.c. in one hour. Average heart beat 153 per minute, an increase of 14 beats to the minute.

Table II. The normal secretion for twenty minutes amounted to 10.8 c.c., or at the rate of one hour, 32.3 c.c.; average heart beat per minute 132. After injection of atropin, gr. $\frac{1}{250}$ hypodermically, the amount secreted in the first twenty minutes amounted to 7.1 c.c. a decrease of 3.7 c.c. in twenty minutes. Average heart rate 138 per minute, an increase of 6 heart beats. The amount secreted in one hour was 16.1 c.c. a decrease of 16 c.c. for one hour. Average heart beat 141 per minute, an increase of 9 heart beats per minute. The amount secreted the following thirty minutes at the rate of one hour was 14.1 c.c. The chemical analysis of Table I shows a diminished solid, ash and potassium⁹ content with an increased volume of fluid per time unit after injection of atropin. From the above observations it would undoubtedly follow that atropin exerts a partial inhibitory influence upon the secretion of cerebrospinal fluid; that is to say, atropin depresses the nervous stimuli of certain secretory cells of the choroid plexus in the same manner as it does other glands of the body dependent upon nervous stimuli for their secretion. Capelleti has shown that on dogs, atropin and hyoscyamin diminished the flow of cerebrospinal fluid, while pilocarpin increased it. Yoshimura states that atropin produces microscopical changes which are a manifestation of the inhibitory influence brought to bear on the secretory activity of the cells. Dixon and Halliburton¹⁰ have found that after the administration of atropin, subsequent injection of choroid extract produces an increase of cerebrospinal flow.

The decrease in secretion of cerebrospinal fluid can be explained by one of two ways: (1) By granting that there is only one type of secretory nerves in the choroid plexus, and that the activity of the nerve endings depends entirely upon the presence of a chemical substance or hormone, and that the hormone is produced by the choroid cells themselves, atropin¹¹ would decrease the flow then, by depressing the cells which give rise to the formation of the hormone. The increase in flow following the injection of choroid extract, after the animal has been atropinized would be due to the mechanical replacing of a substance necessary for the stimulation

⁹ The potassium was determined by the volumetric method of Drushel (cobaltinitrite method), and was not done in duplicate, as the amount of fluid was too small.

¹⁰ Jour. of Physiol., 1913, xlvii.

¹¹ These secretions dependent upon nervous stimuli are depressed; those dependent upon chemical stimuli are unaffected by the action of atropin.

of the cells to secretion. It is not likely that this gland produces its own hormone. We know of no other gland in the body where such a mechanism occurs. It has been shown further that the extract of the brain and cerebrospinal fluid in general paralysis contains a hormone similar to that found in the choroid plexus. (2) It is more plausible to speculate that the gland is supplied with two sets of secretory nerves, namely: those dependent upon nervous stimuli for their action, the remaining ones dependent on chemical stimuli for their activity. The former would explain the diminution in flow after the injection of atropin. The latter would explain the increase after the injection of choroid or brain extract. Dixon and Halliburton suggest that the chemical stimuli or hormone are some part of the product of the brain's metabolism.

SUMMARY OF THE EFFECT OF EPINEPHRIN ON FLOW OF CEREBROSPINAL FLOW. Table I. The normal secretion for thirty minutes amounted to 5.4 c.c. or in terms of sixty minutes 10.8 c.c. Average heart rate 128 beats per minute. After the injection of adrenalin (1 to 1000) m_v subcutaneously, the amount secreted in the first thirty minutes amounted to 3.1 c.c., or in terms of one hour, 6.1 c.c., a decrease of 2.3 c.c. in thirty minutes, or in terms of sixty minutes a decrease of 4.7 c.c. Average heart rate for thirty-five minutes after injection of adrenalin was 150.

The following fifty minutes the secretion at the rate of an hour was 15.2 c.c. Three hours after the injection, the blanching upon the arm becoming smaller, the secretion amounted to 14 c.c. per hour. Five hours after the injection the secretion amounted to 13 c.c. per hour. Six hours later the blanching on the arm had entirely disappeared. The secretion gradually diminished and ceased entirely for fifteen minutes, the child apparently being asleep. The child became restless and the secretion began to flow again. The first five minutes amounted to 1.06 c.c. The collection for the following eighty minutes was 5.9 c.c. Seven hours after the injection the secretion collected in sixty minutes amounted to 17.7 c.c.

The chemical analysis of the fluid following the injection of epinephrin shows such marked variations that it would be stretching a point to attempt an interpretation.

We notice, then, that after the injection of epinephrin the secretion is diminished a little more than one-half in the first thirty minutes. Frazier has likewise reported a marked diminution in his experiments on dogs. What is the explanation? Does epinephrin constrict the cerebral vessels, and by decreasing the blood supply to the choroid plexus diminish the cerebrospinal flow?

The increase in pressure in the circle of Willis after the injection of epinephrin, as is found by Biedl and Reiner, and the decrease in flow from the external jugular vein, reported by Pick, point to a local constriction in the cerebral arterials. In experiments made

upon an isolated brain (in the skull) perfused with an artificial circulation, Wiggers¹² states that the addition of epinephrin causes a diminution in outflow from the organ. He believes the drug constricts the cerebral vessels in the same manner as it does vessels of other organs, and therefore suggests the existence of cerebral vasoconstriction nerves. On the other hand, Bayliss and Hill experimentally could discover no constricting effect of epinephrin on the cerebral vessels. Gerhardt concludes that nothing more than a passive dilatation occurs within the cranium. Dixon and Halliburton, as a result of their experiments on dogs, state that they have never observed constriction of the cerebral vessels from the use of epinephrin, and they challenge the technique as carried out by Wiggers.

Guillard, Huber, and Hunter have demonstrated that the vessels of the brain are provided with perivascular nerve plexuses. But writers as Roy and Gherrington, Hill Wagner¹³ and others from their experimental studies conclude that the cerebral vessels do not possess vasomotor nerves. Masso,¹⁴ as quoted by Howell, has shown by observation upon men with trephine holes in the skull that the constriction of the limbs is always accompanied by dilatation of cerebral vessels. Cushing¹⁵ states that only those vessels of the body that receive nerve fibers from the thoracolumbar cord are constricted by epinephrin. The blood is, therefore, diverted from the organs supplied by the thoracolumbar segment, and as a result the cerebral vessels become passively dilated. Suffice it to say, experimental evidence points to the non-constricting action of epinephrine on the cerebral vessels. Further, Frazier¹⁶ has shown experimentally that ligation of both carotids in dogs, thereby decreasing the blood-supply to the choroid plexus has no retarding influence on the rate of the secretion of cerebrospinal fluid. He has also demonstrated that the injection of saline extracts of certain organs, especially of the liver, kidney, spleen and pancreas, caused a fall in blood-pressure, and at the same time a marked increase in flow of cerebrospinal fluid. Likewise amyl nitrate produced an increase in flow of the fluid. On the other hand, he has shown that the injection of epinephrin caused a rise of blood-pressure, and coincident with this a marked decrease in flow of cerebrospinal fluid. That is to say the general rise in blood-pressure accompanied by an increased flow of blood through the brain, and increased intracranial pressure, is followed by a diminution of cerebrospinal secretion, and the fall in blood-pressure which is accompanied by a decrease in flow of blood through the brain and decreased intra-

¹² *Am. Jour. Physiol.*, 1905, xiv, p. 452.

¹³ Howell, W. H., *Text-book of Physiology*, Philadelphia, 1907, p. 580.

¹⁴ *Ibid.*, p. 579.

¹⁵ *Text-book of Pharmacology and Therapeutics*, Philadelphia, 1910, p. 334.

¹⁶ *The Cerebrospinal Fluid as a Problem in Intracranial Surgery*, *Jour. Amer. Med. Assoc.*, 1914, lxiii, 287.

cranial pressure results in an increased secretion of cerebrospinal fluid.

It would appear that the cerebrospinal fluid which fills the space of the cranial cavity not occupied by vessels and nerves adjusts the mechanism of the circulation of the brain tissue by equalizing pressure. So nature has adjusted, so to speak, through its nervous mechanism, the secretion of the choroid plexus in such a way, that the activities of the cells are diminished when there is a rise in blood-pressure (increased intracranial pressure) and an increase in the activities occurs when the blood-pressure falls (decreased intracranial pressure). There is then a certain inverse relationship between the blood-pressure (intracranial pressure) on the one hand and the secretory activities of the choroid plexus on the other, and this relationship has the characteristics of a purposeful adaptation. Therefore, the diminution of flow which occurs after the injection of epinephrin is to be explained by the inverse relationship between blood-pressure and the secretory activity of the choroid plexus.

The fact that a marked increase of secretion occurred forty minutes after the injection of epinephrin is to be explained on the ground that the action of the drug had been spent¹⁷ by this time and as a result the blood-pressure fell with a corresponding increase in flow of cerebrospinal fluid. I was particularly attracted while making my observations and perplexed at the time to find, when collecting my controls, or when urotropin was given, that the secretion invariably decreased when the child was restless, and increased when asleep. At times the patient would be in a violent anger, striking as I would attempt to collect the fluid, and if the hands were held, would toss, scream, and contract violently every muscle. During the entire procedure we were amazed to find the secretion markedly decreased. At other times, after the child had been asleep for some time, restlessness would cause a momentary increase in flow, which is to be explained upon a mechanical basis. However, if the restlessness existed any length of time the momentary increase would be followed by a decrease in flow for the entire time of restlessness. (See TABLE III). This likewise carries out the inverse relationship between the blood-pressure which rises during restlessness, and falls during quietude and sleep, and the secretory activity of the choroid plexus, and further substantiates the purposeful adaptation theory. In pathological cases, however, this does not hold good. Here we are dealing with a degenerative process which is taking place in the brain tissue, causing an increase in brain metabolism. Thus there is added to the blood stream a superabundance of hormones, which in turn stimulates those cells

¹⁷ The action of epinephrin when injected intravenously is of short duration. When injected subcutaneously it causes a blanching at the point of injection and in large doses the blanching acts as a reservoir, so to speak, for renewed supply.

of the gland dependent upon a chemical stimulus for their activity to hyper-secretion.

We also noticed that there was a marked increase in secretion ten to fifteen minutes after the intake of water; and a very slight change, if any, after the intake of milk. Throughout the entire observations, the pulse rate bore absolutely no relationship to the amount of secretion.

The child was given, on different occasions, large doses of urotropin by mouth, and the cerebrospinal fluid collected in sterile glass tubes at five-minutes intervals for several hours after the intake of the drug. We hope within the near future to publish the results of the appearance and disappearance of urotropin in cerebrospinal fluid, as is found in the case of the patient herein reported.

We wish to express our great indebtedness to Dr. Louis Mutschler, under whose service the child was treated, for kindly permitting us to publish full observations of the case.